REMARKS

Claims 2-9, not 1-9 as stated in the Office Action Summary, are pending in the application. Upon entry of the amendment herein, claims 2-9 remain pending in the application; claim 2 has been amended.

Claim 2, and claims 3-9 dependent therefrom, remain rejected as indefinite "for reason of record." The Examiner maintains that claim 2 omits essential steps; in particular, it is asserted that "a correlation step correlating the 'light energy measured' with the 'peptidoglycan synthesis' is missing and/or not distinctly recited in the rejected claim." In the April 17, 2002 discussion with Applicants' agent, the Examiner confirmed that page 6, lines 16-24 of the instant specification, cited in Applicants' previous response, provides support for the alleged omitted essential steps. The Examiner also affirmed her belief that appropriate language from that specification passage must be inserted into claim 2.

In the interest of expediting prosecution of the application, then, claim 2 has been further amended to recite elements of the defining disclosure cited by Applicants. Language from page 6, lines 9 and 10 has also been incorporated into the claim. The inserted elements are along the lines of those discussed, and agreed upon, by the Examiner and Applicants' agent Furthermore, the amendment of claim 2 meets

all of the criteria for entry of amendments after final rejection; entry of the amendment is respectfully requested. In light of the amendment, the indefiniteness rejection should be withdrawn, and such withdrawal is respectfully requested.

Applicants acknowledge the Examiner's (tacit) withdrawal of all other previous indefiniteness rejections of the claims.

The rejection of the claims under 35 USC §103(a) as being obvious over Elhammer in view of Mengin-Lecreulx et al. and Kohlrausch et al. has been maintained, again "for reason of record." The Examiner maintains that the Elhammer disclosure of the application of SPA in studying cellular processes combined with the alleged teachings of Mengin-Lecreulx and Kohlrausch with regard to peptidoglycan synthesis in *E. coli* would have led one of ordinary skill in the art to the instant invention. Again, Applicants emphatically disagree with the Examiner's assessment.

The Examiner states that "[A]bsent unexpected results, it would have been obvious to have applied" SPA "in detecting peptidoglycan synthesis." However, unexpected results are not the appropriate standard in the present context. The Examiner appears to believe that mere knowledge of the pathway of peptidoglycan synthesis, provided by the secondary references, would have enabled one of skill in the art to fill in the gaps in the teaching of the primary reference, and would somehow have

countered some of the discouraging prior art teachings, thus motivating the skilled artisan to arrive at the instant invention. However, such knowledge provides no guidance for overcoming the obstacles well known in the art at that time, nor does it provide any encouragement to try to overcome said obstacles.

It must be emphasized that the Examiner's assessment of the "obviousness" of the instant invention could only have been arrived at by the use of impermissible hindsight. It must be appreciated that the enzymes used in the assay according to the instant invention are those involved in the final stages of peptidoglycan synthesis (classically referred to as stage 2 and 3 peptidoglycan synthesis where peptidoglycan is the final product) and represent so-called "downstream enzymes." As disclosed on page 3, lines 6-25 of the present application, methods for assaying the (downstream) enzymes have typically relied on paper chromatography, and this is confirmed, for example, in the Mengin-Lecreulx reference (see the experimental section on page 4628, left-hand column.) However, a drawback of using paper chromatography is that it is difficult to control the reaction conditions and, furthermore, it is entirely unsuitable for high throughput screening of compounds.

That the assay of downstream enzymes is recognized in the art to be difficult is illustrated, for example, in a passage

from the first paragraph of the article of Men, et al., J. Am. Chem. Soc. **1998**, *120*, 2484-2485 (copy enclosed), published only a few months before the earliest claimed priority date of the present application:

> Although remarkable progress has been made in characterizing some of the early enzymes in the biosynthetic pathway, the downstream enzymes have proven exceedingly difficult to study. This is partly because the downstream enzymes are membrane-associated, making them intrinsically hard to handle, and partly because substrates for many of the enzymes are not readily available. These problems have impeded the development of active assays suitable for detailed mechanistic investigations of the downstream enzymes.

Bearing in mind that scintillation proximity assay (SPA) technology has been known from U.S. Patent No. 4,568,649 since 1986 (see page 6, lines 4 and 5 of Elhammer), the Examiner's contention that the assay according to the present invention is obvious is simply not credible. If such were the case, it would indeed be very surprising that it was not disclosed before, particularly since there has arguably been a long-felt need in the art for a straightforward and convenient method for assaying the downstream enzymes of the peptidoglycan biosynthetic pathway, particularly a method that can be used with membrane-bound enzymes (as demonstrated in the example of the present

application) and also one that can be adapted for high throughput screening of compounds.

Notwithstanding that the presently claimed invention is nonobvious in view of the above arguments, Applicants present the following additional arguments in support of nonobviousness.

In arguendo, even if the prior art could be considered to provide a suggestion of the presently claimed invention (which it cannot), at the very most this could only possibly be considered to make it obvious to try to obtain the present invention, rather than making the present invention obvious to do.

It is well-established that the standard of nonobviousness under 35 U.S.C §103 is *not obvious to try, but obvious to do*. (See In re O'Farrell, 853 F.2d 894, 7USPQ2d 1673 (Fed. Cir. 1988).) As determined in O'Farrell, an invention that is obvious to try is nevertheless nonobvious when the prior art makes it obvious to explore a new technology or general approach, for example SPA, that seemed to be a promising field of experimentation, but where the prior art gives only general guidance as to the particular form of the claimed invention or how to achieve it. The courts have also rejected an "obvious to experiment" approach; selective hindsight is no more applicable to the design of experiments than it is to the combination of

prior art teachings. (See In re Dow Chem. Co. 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).)

In view of Applicants' arguments in the previous sections, the cited prior art does not make the presently claimed invention obvious to do. A further indication that the prior art fails to make the presently claimed invention obvious to do is that the subject matter of the primary reference, Elhammer, and that of the present invention are only remotely related. Specifically, in contrast to the presently claimed invention, Elhammer does not relate at all to enzymes, such as bacterial GlcNAc-transferase, required for peptidoglycan synthesis. Furthermore, the peptidoglycan synthetic pathway is found only in bacterial (prokaryotic) systems. Elhammer, however, relates to the eukaryotic enzyme GalNAc-transferase, which catalyzes the transfer of N-acetylgalactosamine to serine and threonine residues of polypeptides to form glycosylated proteins. (See Elhammer, page 2, line 6 - page 3, line 8.)

Furthermore, Elhammer actually teaches away from the use of SPA when a membrane-bound enzyme is involved in the catalytic process or pathway for which an assay is desired. (See Elhammer, page 3, lines 9-15.) This makes embodiments of the present invention which utilize membrane-bound transferase *not even* obvious-to-try.

It must also be appreciated that Elhammer provides an assay for the activity of a single eukaryotic enzyme involved in a one-step process, the *O*-glycosylation of polypeptides. This enzyme is not part of the complex, multistep prokaryotic peptidoglycan synthesis pathway of the instant invention. Thus, Elhammer only teaches and provides motivation for a reductionist approach, focused on identifying inhibitors of the single enzyme. In contrast, the presently claimed invention employs a multi-enzyme, system-based approach by which compounds which inhibit any single activity, or even multiple catalytic activities, of the subject part of the peptidoglycan synthesis pathway can be identified. The system-based approach of the present invention provides the following advantages not provided by or suggested by the prior art.

First, when, as for the case of the present invention, the goal is to obtain inhibitors of the production of a product formed by a synthetic pathway, it is far more efficient to simultaneously screen for inhibitors of multiple parts of the pathway rather than to screen for inhibitors of each enzymatic activity separately. There is no suggestion of this advantage whatsoever in any of the cited prior art references.

Second, by measuring the success of inhibition of production of the end product, where it is the production of the end-product that is important (in this case, necessary for

growth and survival of bacterial pathogens), the assay of the present invention, in contrast to single-enzyme types of assays, assures that the effect of an inhibitor identified by the assay on an enzyme within the pathway segment is not countered by regulation of another enzyme, so that production of the end-product is unaffected.

Third, by employing an entire segment of the peptidoglycan synthetic pathway, the presently claimed assay provides for the possibility of identifying indirect inhibitors of enzymes within the subject pathway segment, i.e., inhibitors that do not directly inhibit a subject enzyme but that interfere with, for example, the allosteric regulation of the enzyme by another enzyme or by the upstream or downstream product of another enzyme. These sorts of inhibitors are not identifiable by a single-enzyme type of assay.

In view alone of the *per se* advantages described above, which are in no way suggested by or appreciated in the cited prior art, the presently claimed invention is nonobvious.

For all of the reasons set forth above, the present invention is nonobvious over the cited prior art. In summary, the Examiner has read far more guidance into the prior art than is warranted, and this is borne out by the facts, for example, that 1) the assay described in the primary reference and that instantly claimed cannot be said to be that similar and 2)

despite the guidance alleged by the Examiner, no one in the ten years prior to Applicants' filing of the application is on record as having thought of developing the assay claimed in the instant application. In light of the actual state of the prior art at the time of filing, which included disclosure actually teaching away from the instant invention, and in light of the advantages provided by the instant invention, said invention cannot be considered obvious in view of the cited prior art or in view of any other knowledge at the time.

In light of the amendments herein and the above arguments, the claims describe the invention with the definiteness required by statute, and the claimed subject matter is patentably distinct from the knowledge in the field at the time of filing. Reconsideration and allowance of pending claims 2-9 are respectfully requested. Should any other matters require attention prior to allowance, it is requested that the Examiner contact the undersigned.

The Assistant Commissioner is hereby authorized to charge any fees which may be due for any reason to Deposit Account No. 23-1703.

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Respectfully submitted,

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Enclosure